



TITLE:

Effect of Intravenously Administered Fat Emulsion on Liver Function in Totally Depancreatized Dogs

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Effect of Intravenously Administered Fat Emulsion on Liver Function in Totally Depancreatized Dogs

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Abstract

Total Pancreatectomy was performed under nembutal anesthesia in 16 adult mongrel dogs after a 24-hour fast, and the depancreatized dogs were given parenteral nutrition containing fat emulsion. Serum lipids, intravenous fat tolerance and post-heparin lipolytic activity were determined and liver biopsy was done to demonstrate the presence or absence of fatty liver. The animals were divided into three groups: group A (n=6) received fat emulsion 1 g/kg/day; group B (n=5), fat emulsion 2 g/kg/day; and group C (n=5), no fat emulsion. Blood levels of cholesterol and phospholipid were increased in group B, while only a mild elevation of the blood triglyceride (TG) level was noted in group A. In group C, cholesterol and phospholipid levels were decreased, and hypoglycemia was liable to occur. The rate of disappearance of blood fat (K₂) was decreased two weeks after surgery in group B, but there were no significant change in the other two groups. These findings suggest that if insulin is present, the administration of fat emulsion will not cause fatty liver.

Introduction

In combatting malnutrition due to lack of endocrine and exocrine pancreatic function after total pancreatectomy, carbohydrates and amino acids are generally provided by hyperalimentation soon after surgery, but fat emulsion is rarely given. It seems that after total pancreatectomy the primary concern is blood sugar control, and fat is rarely given because of abnormal lipid metabolism due to insulin and glucagon deficiencies. Furthermore, the occurrence of fatty liver after total pancreatectomy^{3,9)} seems to have restrained the administration of fat. It has been accepted that fatty liver develops from a deficiency of essential fatty acids¹⁾. Therefore, fat administration is important and

Key words: Fat emulsion, Depancreatized dogs, Fat tolerance test, Lipoprotein Lipase.

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should be considered from the point of view of caloric supplementation, liver cell membrane stabilization, and alleviation of respiratory load⁴⁾. There have been few studies on fat administration in the early stage after total pancreatectomy.

Materials and Methods

1) Preparation of an experimental model and course of experiment

Sixteen adult male mongrel dogs weighing 12 to 16 kg were used. A catheter (Atom 6) inserted for about 5 cm into the right external jugular vein with a cutdown was passed subcutaneously to the dorsal region of the neck and fixed to the testing apparatus. Several days later, liver function, fat tolerance, and postheparin lipolytic activity (PHLA) were tested. Total pancreatectomy was then performed under nembutal (30 mg/kg) anesthesia, with preservation of the duodenum and pancreaticoduodenal arteries and veins. For four weeks surgery the animals were maintained on IVH with free access to water only. Fat tolerance and PHLA tests were performed 1, 2, 3, and 4 weeks after surgery; liver biopsy was done 2 and 4 weeks after surgery.

2) Fat tolerance test (FTT)

Under nembutal anesthesia, 1 ml/kg of fat emulsion (10% Intrafat) was injected rapidly intravenously via the IVH route, and blood was drawn with heparin from the peripheral veins every 5 min for 40 min. The blood samples were centrifuged at 4°C, 600 r.p.m. for 10 min, and the plasma was measured by a micronephrometer^{13,22)} to calculate K_2 values (fractional removal rate) by the Hallberg method⁷⁾.

3) PHLA assay

Three hours after the start of the FTT, 100 U/kg of heparin was injected intravenously under nembutal anesthesia; 10 min later, blood was drawn, 0.1 M sodium citrate was added, and the sample was centrifuged at 3000 r.p.m for 15 min at 4°C; the plasma obtained was frozen and stored at -20°C. At the time of assay, the frozen samples were thawed assayed for lipoprotein lipase (LPL) by the method of BAKER et al⁵⁾. For the emulsification of the substrates, 500 mg (0.565 mmol) of triolein, 7.5 ml of 1 M tris-HCl (PH 8.3), 4.0 ml of 0.69% (w/v) Triton X-100, and 5.5 ml of distilled water were put into a plastic bottle for sonication (200 w, 2 A, 8 min). To 6.4 ml of emulsion were added 4.0 ml of 5% bovine serum albumin (FFA free), 1.4 ml (60 mmol/l) of fresh human serum, 1.2 ml of NaCl, and 7.0 ml of distilled water to activate the substrate. To 1.0 ml of this substrate solution 0.1 ml of testing plasma was added, and the mixture was incubated at 37°C for 60 min; it was then shaken and immersed in ice water. The FFA were assayed by an enzyme method. The unit was expressed as the quantity of FFA (umol FFA/ml/min) hydrolyzed per 1 ml of plasma in one min.

4) Intravenous hyperalimentation (IVH) (Table 1)

After surgery the animals were divided into three groups (6 in group A, 5 in group B and 5 in group C) and maintained for 4 weeks.

Group A: The animals were given glucose 4 g/kg/day, amino acid 1 g/kg/day, fat 1 g/kg/day, regular insulin 1 U/5 g of glucose/day, and heparin 300 U/day for three days after surgery. From the 4th day on glucose was increased to 6 g and amino acid to 2 g, and regular insulin was changed to 1 U per 5-7.5 g of glucose. On the day of testing, fat and heparin were not given.

Group B: For three days after surgery glucose 2 g/kg/day, amino acid 1 g/kg/day, fat 2 g/kg/day, regular insulin 1 U/2.5 g glucose/day, and heparin 600 U/day were administered. From the

Group	Content of TPN solution	During 3 days after surgery	4 days after surgery	At the day of examination
A Group n = 6	Glucose (g/kg)	4	6	6
	Amino acid (g/kg)	1	2	2
	Lipid (g/kg)	1	1	0
	Glucose (g) Insulin (u)	5	5~7.5	5~7.5
	Heparin (u)	300	300	0
B Group n = 5	Glucose (g/kg)	2	4	4
	Amino acid (g/kg)	1	2	2
	Lipid (g/kg)	2	2	0
	Glucose (g) Insulin (u)	2.5	3.33	3.33
	Heparin (u)	600	600	0
C Group n = 5	Glucose (g/kg)	6	8	4
	Amino acid (g/kg)	1	2	2
	Lipid (g/kg)	0	0	0
	Glucose (g) Insulin (u)	5	5	5
	Heparin (u)	0	0	0

Table 1. Composition of infusion solution.

4th day on glucose was increased to 4 g/kg and amino acid to 2 g/kg, and regular insulin was changed to 1 U per 3.3 g of glucose. On the day of testing fat and heparin were not given.

Group C: For three days after surgery glucose 6 g/kg/day, amino acid 1 g/kg/day, and regular insulin 1 U/5 g of glucose/day were given. From the 4th day on glucose was increased to 8 g/kg and amino acid to 2 g/kg; regular insulin 1 U per 5 g of glucose was continued. On the day of testing glucose and insulin were reduced to half the former amount.

Each group was given glucagon 0.1 ml/day and water 45–50 ml/kg/day. Infusion was performed by an infusion pump at a constant rate for each pack.

5) Liver function test, lipid test and liver biopsy

One, 2, 3, and 4 weeks after surgery, liver function tests (GOT, GPT, ALP, LDH and total bilirubin) and lipid tests (total cholesterol, TG, phospholipid, FFA, total lipids, blood sugar, 3-hydroxybutyric acid (3-OHBA), albumin and retinol-binding protein (RBP)) were done. Liver biopsy specimens were examined with hematoxylin-eosin and Sudan red 0 stains.

Statistical evaluation was done with Student's t-test, and p values less than 0.05 were considered significant.

Results

1) Blood glucose levels

In group A, blood glucose levels were increased significantly from 92 ± 8.9 mg/dl before surgery to 351 ± 112 , 297 ± 81 , 314 ± 55 , and 359 ± 79 mg/dl at 1, 2, 3, and 4 weeks after surgery, respectively, (1st week: $p < 0.05$; from 2nd week on: $p < 0.01$), while no marked changes in blood glucose levels were observed in groups B and C. This seemed to be due to a higher ratio of insulin dose (U) to

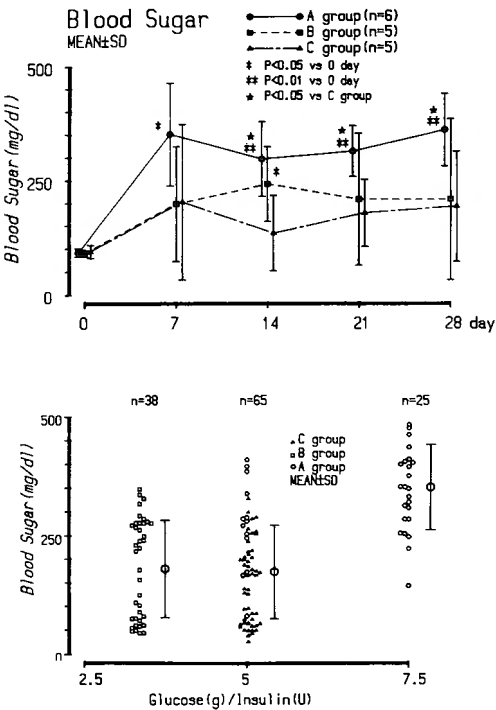


Fig. 1 Upper: Changes of blood glucose levels after surgery.
Lower: Relationship between blood glucose and insulin dose to glucose dose.

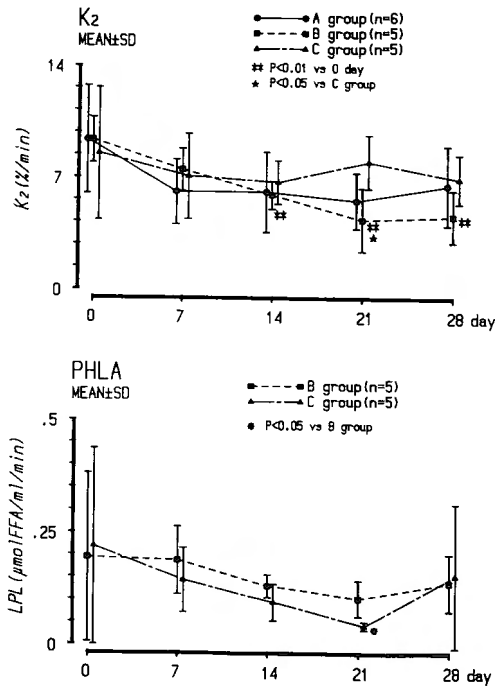


Fig. 2 Upper: Changes of K₂ values after surgery.
Lower: Changes of LPL values after surgery.

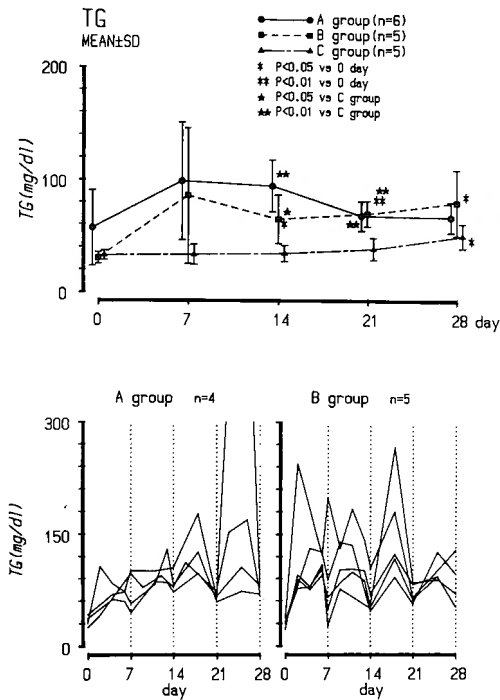


Fig. 3 Upper: Changes of TG values after surgery. Lower: Postoperative changes of TG values in groups A and B.

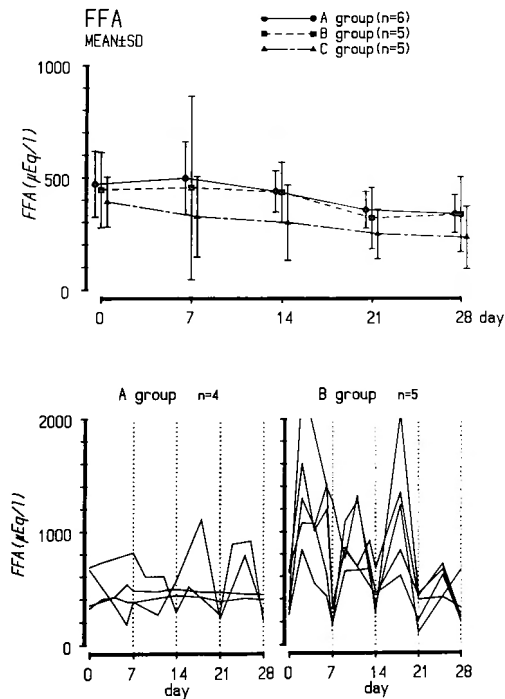


Fig. 4 Upper: Changes of FFA values after surgery. Lower: Postoperative changes of FFA values in groups A and B.

glucose dose (g) in group A (Fig. 1).

2) Fat tolerance test; K_2 Values

K_2 values were decreased in group B only, from $9.3 \pm 1.4\%/min$ before surgery to 5.9 ± 0.9 , 4.3 ± 2.0 and $4.6 \pm 1.6\%/min$ ($p < 0.01$) at 2, 3, and 4 weeks after surgery, respectively; no significant changes were observed in the other groups (Fig. 2).

3) Postheparin lipolytic activity (PHLA)

The PHLA test on lipoprotein lipase (LPL) was done only in groups B and C. Three weeks after surgery LPL levels in group C were significantly lower ($p < 0.05$) than in group B (Fig. 2).

4) Serum lipid

(1) In group A TG levels were elevated 1 and 2 weeks after surgery, but not significantly so. Group B showed a mild but significant elevation: from 30 ± 5 mg/dl before surgery to 65 ± 22 , 70 ± 11 and 80 ± 29 mg/dl at 2, 3, and 4 weeks, respectively, after surgery (2nd and 4th week: $p < 0.05$; 3rd week: $p > 0.01$). Group C showed an elevation at 4 weeks ($p < 0.05$). TG continued considerably higher during the administration of fat emulsion than on the day of discontinuation (Fig. 3), apparently because the TG of the fat emulsion was measured.

(2) No significant changes in FFA levels were observed in any group on the day of testing. However, FFA levels were considerably higher during the administration of fat emulsion than on the day of discontinuation (Fig. 4), probably because the TG in the fat emulsion was decomposed.

(3) In group B total cholesterol levels were significantly increased from 109 ± 10 mg/dl before surgery to 212 ± 34 , 220 ± 31 , 241 ± 35 , and 284 ± 19 mg/dl at 1, 2, 3, and 4 weeks, respectively, after surgery ($p < 0.01$). No significant increase was observed in group A. Group C showed a

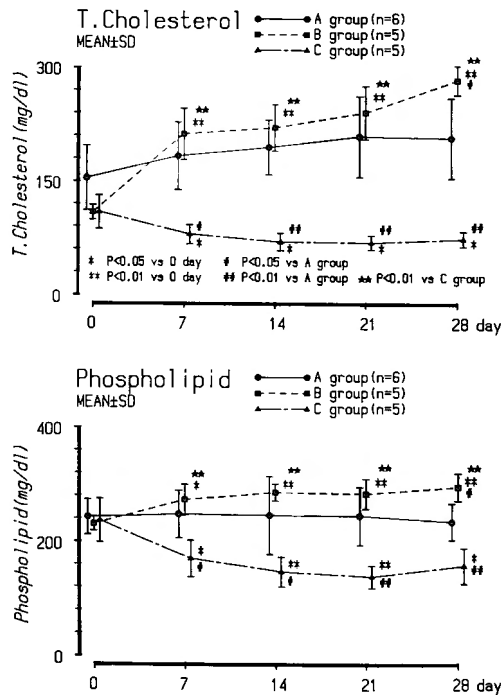


Fig. 5 Upper: Changes of total cholesterol levels after surgery. Lower: Changes of serum phospholipid levels after surgery.

significant decrease: from 109 ± 22 mg/dl before surgery to 80 ± 12 , 70 ± 11 , 69 ± 9 , and 74 ± 10 mg/dl, respectively, at 1, 2, 3, and 4 weeks after surgery ($p < 0.05$).

- (4) No appreciable changes in phospholipid levels were observed in group A, while group B showed a significant increase: from 231 ± 12 mg/dl before surgery to 272 ± 27 , 285 ± 15 , 283 ± 26 , and 295 ± 24 mg/dl at 1, 2, 3, and 4 weeks, respectively, after surgery (1st week: $p < 0.05$; from 2nd week on: $p < 0.01$). Group C showed a significant decrease: from 237 ± 38 mg/dl before surgery to 170 ± 32 , 146 ± 26 , 138 ± 20 , and 150 ± 31 mg/dl at 1, 2, 3, and 4 weeks after surgery, respectively, (1st and 4th weeks: $p < 0.05$; 2nd and 3rd weeks: $p < 0.01$) (Fig. 5). The values were higher during the administration of fat emulsion than on the day of discontinuation, and this trend was more pronounced in group B.
- (5) There was no marked elevation in blood levels of ketone bodies (3-hydroxybutyric acid: 3-OHBA). However, when infusion was suspended because of temporary difficulties, high value of more than $100 \mu\text{mol/l}$ were observed occasionally. During the administration of fat emulsion, there was a significant correlation between 3-OHBA and FFA ($r = 0.74$, $p < 0.01$) and also between 3-OHBA and TG ($r = 0.66$, $p < 0.01$), presumably because the TG of the fat emulsion turned into FFA, a portion of which turned further into ketone bodies.
- (6) Among the liver function tests, GPT was high about 1 week after surgery, began to fall at about 2 weeks and was normal at 4 weeks. ALP levels tended to rise after surgery: in group A from 2.6 ± 0.9 (KAU) before surgery to 7.9 ± 2.2 and 8.2 ± 1.5 (KAU) at 1 and 2 weeks, respectively, after surgery (both weeks: $p < 0.01$); in group C, from 2.4 ± 0.8 (KAU) to 6.4 ± 2.1 , 5.2 ± 1.6 , and 7.4 ± 3.4 (KAU) at 1, 2, and 3 weeks, respectively, (1st week: $p < 0.01$; 2nd and

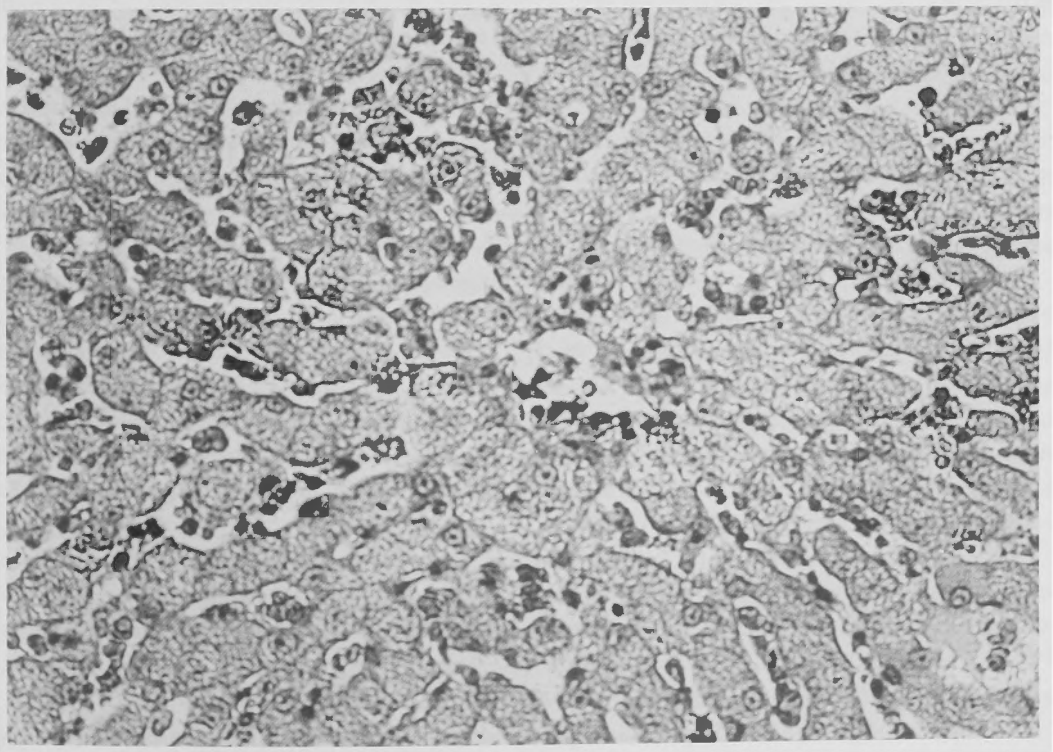


Fig. 6 Specimen of liver biopsy ($\times 100$).

3rd week: $p < 0.05$). Some group B dogs also showed a marked increase of ALP levels after surgery.

- (7) Liver biopsies showed fatty liver in one dog in group A. In this case, infusion had been rather frequently interrupted because of difficulties with the catheter, and the fatty liver in this case seemed to have developed because of an insufficiency of insulin. Fatty liver was not found in any of the other animals of groups A, B or C (Fig. 6).

Discussion

In the correction of malnutrition due to lack of endocrine and exocrine pancreatic function after total pancreatectomy, carbohydrates and protein are generally administered, while fat emulsion is rarely given because of the possible occurrence of fatty liver after total pancreatectomy. However, it has been reported that a deficiency of essential fatty acids contributes to the development of fatty liver. Using dogs, we investigated the feasibility of administering fat emulsion after total pancreatectomy.

In group A hyperglycemia persisted after surgery, suggesting insulin deficiency, but blood ketones were rarely elevated, and when fat emulsion infusion was discontinued, FFA levels decreased instead of increasing. This suggests a lowered decomposition of fats pooled in adipose tissues. It has reported that a relatively substantial volume of insulin is required to start carbohydrate metabolism: 5 to 10 times the volume required to start lipid metabolism¹⁹). It appeared, therefore, that the insulin volume in group A was adequate for lipid metabolism, but insufficient for the control of blood glucose. When glucose is supplied to increase calories, it is necessary to increase the insulin dose simultaneously. In this respect, fat emulsion as a calory source, could contribute to better control of blood glucose.

In the fat tolerance test, K_2 values, which are biphasic and represent a gradient of exponential functional decreasing curves, showed the rate of elimination of TG when the blood TG level was constant, and heparin increased the rate of elimination of fat emulsion and chylomicrons from the blood stream⁷). This constant value represents the critical concentration of BOBERG et al⁷), at which the binding of lipoprotein lipase activity (LPL) and TG in blood vessel walls is saturated⁶).

If fat emulsion is administered when K_2 values are low, fat particles which were not decomposed by LPL are taken up for disposal in the reticuloendothelial system in the liver and spleen, and early fatty acid oxidation cannot be expected. Therefore, if fat emulsion is administered when K_2 values are low, it is probably necessary to reduce the dose or to administer heparin to induce fat decomposition by LPL. Heparin releases LPL into the blood to increase contacts between LPL and fat particles, resulting in an acceleration of the decomposition of TG. Although one report has stated that K_2 values are elevated when fat emulsion is given for several days¹⁰), it is generally accepted that K_2 values are lowered as TG levels increase^{7,14,24}).

In the present study K_2 values decreased significantly from the 2nd week on in group B only, while TG levels rose significantly; no elevation of K_2 values was observed during the administration of fat emulsion. It has also been reported that K_2 levels are not correlated with fatty acid oxidation^{8,17}), and its clinical significance is open to contention¹¹); however, K_2 seems to be useful in the administration of fat emulsion without causing hypertriglyceridemia.

LPL in the PHLA test is a rate-limiting enzyme for TG decomposition. In patients treated with total pancreatectomy LPL levels were reported to be within the normal range after the acute

stage had subsided¹²⁾. Our study showed a wide variation in preoperative LPL values and no significant change between pre- and post-operative LPL values. Our findings that both K_2 and LPL values were lowered slightly after surgery suggest that lipid metabolism is decreased after total pancreatectomy. In group B the postoperative values of total lipid, total cholesterol, phospholipid and TG were increased. The increase in TG values was slight in both A and B groups, and they returned rapidly to normal after discontinuation of the administration of the fat emulsion. TG levels seemed to be controllable by increasing the dose of heparin. On the other hand, attention should be called to the increase in cholesterol and phospholipid levels. The significant positive correlation between total lipid and total cholesterol noted in our study supports the view that the increase of total lipid is due mainly to total cholesterol. It has been reported that the administration of fat emulsion causes hypercholesterolemia and that this increase of cholesterol is not due to increased synthesis in the liver but to migration from body tissues²⁾. Another study showed that while the intestinal administration of fat emulsion in humans did not cause any abnormalities of serum lipids, the intravenous administration increased LPL, with a resulting increase of total cholesterol and phospholipid²³⁾. The relationship between the administration of fat emulsion and the occurrence of hypercholesterolemia and hyperphospholipidemia has not yet been elucidated, but the latter is not specific to total pancreatectomy, and it is still unclear whether it should be left untreated.

Levels of FFA and decomposed products of TG in fat emulsion, were not significantly different on the day of testing from the preoperative levels, but they were markedly elevated during the administration of fat emulsion. These findings suggest that exogenous TG was decomposed by LPL and part of it was released into the blood as FFA. It is obvious that the elevation of FFA levels was not due to accelerated decomposition of fat pooled in adipose tissues, because FFA levels decreased when the administration of fat emulsion was discontinued. Further studies are needed to determine whether fat emulsion is not utilized and accumulates in the reticuloendothelial system of the liver and spleen, or whether it does not accumulate in the form of metabolites as in patients with fatty liver. In this study, liver biopsies were done to determine the presence or absence of fatty degeneration; no abnormal fatty accumulation was seen, such as that found in fatty liver. It has been reported that fatty liver occurs when the insulin dose is insufficient or is decreased abruptly after total pancreatectomy³⁾. Fatty liver also occurs during long-term infusions which do not include fat, and it is said that this is because the synthesis of VLDL in the liver is reduced because of the decreased synthesis of phospholipid resulting from the deficiency of essential fatty acids¹⁾. Fat emulsion seems to be able to suppress the development of fatty liver, when it is given as essential fatty acids or yolk phospholipid.

Liver function tests showed a transient increase in GOT and GPT within the first 2 weeks. The GPT level, especially, was elevated in some dogs in each group, but it returned to normal with time. It has been reported that long-term administration of high doses of fat emulsion increases ALP and total bilirubin levels²⁾. In our study, however, elevation of ALP and total bilirubin levels was observed in group C, which did not receive fat emulsion. Thus, other factors seem to be responsible for the changes in liver function tests.

Glucagon was administered to prevent hypoglycemia. Glucagon exerts its hyperglycemic action at a dose of 0.01 mg injected intravenously in adult humans¹⁸⁾. In dogs, glucose release into circulating blood is demonstrated even at a dose of 0.05 $\mu\text{g/kg}$ ¹³⁾.

Even if the dose of glucagon is adequate and if the control of blood glucose is poor, the hyperglycemic action of glucagon is weak because there is little liver glycogen¹⁶⁾. Therefore, hypoglycemic attacks occur not only because of glucagon deficiency. It has been reported that in

dogs intestinal glucagon is identical with pancreatic glucagon²⁰⁾, but another report has shown that, although extrapancreatic glucagon, if uncontrolled by insulin, is released in excess after total pancreatectomy, it cannot compensate for the function of pancreatic glucagon because it is suppressed immediately by insulin²¹⁾. Therefore, the administration of glucagon is essential.

Heparin was administered to increase the blood LPL level and accelerate the decomposition of fat emulsion by the method of ZAIDAN et al²⁵⁾. Before fat emulsion is given to humans, the dosage of insulin, glucagon, heparin and carnitine needs further investigation.

Conclusion

The elevation of blood cholesterol and phospholipid levels was mild at a dose of fat emulsion of 1 g/kg/day. Although the rate of disappearance of the fat emulsion decreased slightly, elevation of the TG level was only slight. No marked increase of ketone bodies was noted. Under insulin control, fatty liver did not develop. These results indicate that the administration of fat emulsion is feasible and deserves further investigation. The decrease of cholesterol and phospholipid, which is observed when fat emulsion is not given, can be suppressed by the administration of fat emulsion. Although it cannot be said conclusively that the insulin dose can be reduced, there was less incidence of hypoglycemia in the animal groups which were given fat emulsion. This seemed to be due largely to a lower insulin requirement.

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和文抄録

脾全摘後における脂肪乳剤が肝機能に及ぼす影響について

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脾全摘後には脾内外分泌機能の脱落により, 糖質, 蛋白, 脂質代謝異常に基づく栄養不良が問題となり, 糖蛋白の投与は行われてきたが脂肪乳剤の投与は脾全摘後の脂肪肝の発生の見地から敬遠されてきた。しか

しながら, 必須脂肪酸の欠乏により脂肪肝の発生を促すとも言われており, 脂肪乳剤の投与が肝機能に及ぼす影響について脾全摘犬を用いて検討した。